

## ORIGINAL ARTICLE

# Esophageal gastrointestinal stromal tumor: report of 7 patients

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### Abstract

**Abstract Purpose:** To evaluate imaging features of esophageal gastrointestinal stromal tumors (GIST) with clinical and histopathologic correlation and imaging follow-up. **Materials and methods:** In this institutional review board-approved, Health Insurance Portability and Accountability Act-compliant retrospective study, 14 patients with pathologically proven esophageal GIST seen from January 2001 to October 2011, 7 patients (4 women; mean age 70 years, range 56–87 years) who had imaging of primary tumor and follow-up imaging at our institution were included. Imaging studies were evaluated by 3 radiologists in consensus. Location, size and imaging features of primary tumor and metastases, if any, were recorded, and correlated with pathologic (histopathologic subtype, presence of necrosis, mitotic rate, immunohistochemical profile) and clinical (treatment-related changes, distant spread and outcome) parameters. **Results:** Of 7 tumors, 5 were located in the lower esophagus and 2 in mid-esophagus. Four were intraluminal, 2 were exophytic, and 1 was intramural. All 7 patients underwent computed tomography (CT); tumors appeared as well-circumscribed, hypoattenuating masses showing mild enhancement, with mean size of 5.7 × 4.2 cm. Necrosis and calcification were seen in 1 tumor each. Five patients underwent fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT. GISTs were FDG avid with mean standardized uptake value (SUV)<sub>max</sub> of 9.5 (4.5–12.3). All tumors were positive for KIT (7/7) and CD34 (6/6). Distant metastases to liver and pleura were seen in 1 patient. On imatinib treatment, the tumors responded with decreased attenuation values and unchanged size on CT, and decreased SUV<sub>max</sub> of primary tumor and metastases on FDG-PET/CT. **Conclusion:** Esophageal GISTs are well-circumscribed, FDG-avid, hypoattenuating masses that can metastasize to liver and pleura, and respond to imatinib treatment with decreased attenuation value on CT and decreased SUV<sub>max</sub> on FDG-PET/CT.

**Keywords:** *Gastrointestinal stromal tumor; esophageal; CT; FDG-PET/CT.*

### Introduction

Gastrointestinal stromal tumors (GISTs), the most common mesenchymal malignancy of the gastrointestinal tract, account for up to 3% of all gastrointestinal neoplasms and 5.7% of sarcomas<sup>[1,2]</sup>. Traditionally, GISTs were classified as smooth muscle tumors, formerly

designated leiomyomas, leiomyoblastomas, and leiomyosarcomas. GISTs were identified as a distinct entity in 1983, described as cellular spindle cell or epithelioid tumors<sup>[3]</sup>. The pathogenesis and molecular basis of GISTs were understood only recently. Approximately 80% of GISTs are associated with activating mutations of the *KIT* gene, which encodes a tyrosine kinase

receptor<sup>[4]</sup>, and another 5–7% of GISTs harbor activating mutations in *platelet-derived growth factor receptor- $\alpha$*  (*PDGFRA*)<sup>[5]</sup>. In general, the malignant potential can be predicted based on the mitotic rate and size of the primary tumor<sup>[6]</sup>. The stomach is the most common site of origin of GISTs, followed by the small bowel, colon and rectum<sup>[7]</sup>. The esophagus is the least common site, accounting for <1% of all GISTs<sup>[8]</sup>. The most important differential diagnosis of esophageal GIST is leiomyoma, which is much more common than GISTs. This distinction is critical, because esophageal GISTs tend to pursue an aggressive clinical course, whereas leiomyomas are entirely benign<sup>[7,9]</sup>.

The literature on esophageal GISTs is limited, mainly comprising case reports<sup>[10–13]</sup> and only a few case series<sup>[9,14]</sup>. To the best of our knowledge, there are no series focusing on the imaging appearance of esophageal GISTs. The purpose of this study was to evaluate the imaging features of esophageal GISTs with clinical and histopathologic correlation and imaging follow-up.

## Materials and methods

### *Subjects*

In this institutional review board-approved, Health Insurance Portability and Accountability Act-compliant retrospective study, the electronic medical records of 14 patients with pathologically proven esophageal GIST who were seen at our institution from January 2001 to October 2011 were reviewed to identify patients who had baseline and follow-up imaging at our institution. Patients who did not have imaging studies or adequate histopathologic and immunohistochemical evaluation at our institution were excluded. Seven patients met the inclusion criteria and were included in the study.

### *Imaging studies*

A systematic review of all available imaging studies, including the baseline and follow-up studies, was performed by 3 radiologists in consensus. The location (intraluminal, intramural or exophytic), size (largest dimension in 2 orthogonal planes), shape (round, oval, lobulated or other) and outline (well or ill defined) of the esophageal GISTs were recorded. Most patients had undergone computed tomography (CT) and/or [<sup>18</sup>F]fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT. The CT attenuation and homogeneity (homogeneous versus heterogeneous) of the tumor was noted. Other features, such as the presence or absence of areas of necrosis, calcification, locoregional or distant metastases at presentation were noted. On FDG-PET/CT, the FDG avidity of the tumor (standardized uptake value (SUV)<sub>max</sub>) and the presence of distant metastases were recorded.

### *Histopathologic and clinical correlation*

The histology was reviewed by a pathologist with expertise in GIST. The following pathologic features were recorded: morphologic subtype, presence or absence of necrosis, mitotic rate, and immunohistochemical profile. Owing to the rarity of esophageal GISTs, unlike GISTs of more common sites (e.g., stomach and small intestine), site-specific prognostic factors have not been formally established. Most reported esophageal GISTs are clinically aggressive, although a small subset of cases (particularly small tumors with a low mitotic rate) have pursued a benign course. Therefore, for the purposes of this study, the tumors were dichotomized into low risk (if <5 cm in size and <5 mitoses per 50 high power fields (HPF)) and high risk (either  $\geq 5$  cm or  $\geq 5$  mitoses per 50 HPF). Electronic medical records were reviewed to note the clinical features including primary presentation, treatment offered, recurrence or metastasis-free interval and outcome. These features were correlated with imaging findings to note any treatment-related changes on imaging.

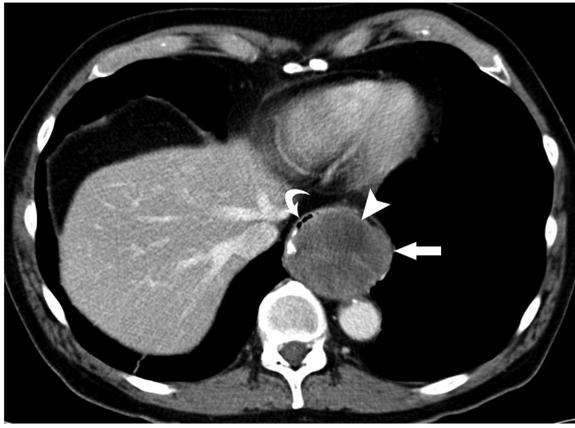
### *Follow-up imaging*

The follow-up imaging studies were evaluated for the presence of recurrent or metastatic disease. Any post-treatment changes in the imaging appearance of the primary tumor and/or metastases were noted. For FDG-PET/CT studies, the change in FDG avidity and SUV<sub>max</sub> between baseline and follow-up imaging was recorded.

## Results

### *Subjects*

The patient population consisted of 4 women and 3 men, with a mean age of 70 years (range 56–87 years). Three patients presented with recurrent cough. In 2 of these patients, the esophageal GIST was initially not detected on chest radiographs. All 3 patients were initially treated for upper respiratory tract infection. When symptoms persisted, further imaging of the chest was performed with CT, which identified the tumor. One patient had longstanding symptoms suggestive of gastroesophageal reflux disease and was initially treated with proton pump inhibitors. The symptoms recurred after initial response, prompting endoscopy, which revealed the tumor in the lower esophagus. Another patient had a history of colon and laryngeal cancer without evidence of metastases. His esophageal GIST was initially detected as a slowly growing esophageal mass before being confirmed by biopsy. In 1 patient, the tumor was detected incidentally on pulmonary CT angiography performed for suspected pulmonary embolism. Esophageal GIST in 1 patient was diagnosed on upper gastrointestinal



**Figure 1** A 71-year-old man with esophageal GIST. Axial image from a contrast-enhanced CT scan demonstrates a hypoattenuating well-circumscribed mildly enhancing intraluminal mass in the lower esophagus (arrow). Note subtle low attenuation area of necrosis within the mass (arrowhead). Compressed lumen of the esophagus containing small amount of oral contrast is seen (curved arrow).

endoscopy performed for evaluation of intermittent dysphagia.

### *Imaging features*

In total, 7 CT examinations and 4 FDG-PET/CT studies of primary untreated esophageal GISTs were reviewed. All of the patients underwent CT of the chest. Of the 7 patients, the tumors were located in the lower esophagus in 5 patients (Fig. 1) and in the mid-esophagus in 2 (Fig. 2). On imaging, the tumors were intraluminal in 4 patients (Fig. 1), exophytic in 2 (Fig. 2), and intramural in 1 patient. The mean tumor size was  $5.7 \times 4.2$  cm, with size ranging from 3.1 to 7.9 cm in the long axis and from 1.8 to 6.5 cm in the short axis. All the primary tumors appeared as round to oval well-defined masses with smooth sharp outlines (Figs. 1, 2), were iso- to hypoattenuating compared with the muscle, and showed mild enhancement on contrast-enhanced CT (Fig. 1). Six of 7 tumors were homogeneous (Fig. 2), and one showed the presence of central necrosis (Fig. 1). Peripheral calcification was present in 1 tumor (Fig. 2). None of the tumors showed evidence of hemorrhage. Baseline FDG-PET/CT was performed in 5 of 7 patients. All the tumors were FDG avid (Fig. 2), with mean  $SUV_{max}$  of 9.5 (4.5–12.3).

Distant metastases were present in 1 patient at presentation (Fig. 2). This patient had hypodense liver metastases that measured 3–4 cm in size. The same patient also had pleural-based metastases. All the metastatic lesions were FDG avid ( $SUV_{max}$  7.6–8.6,  $SUV_{max}$  of the primary tumor, 10.3) (Fig. 2). Subcentimeter pulmonary nodules were present in 1 patient; however, these were incompletely characterized on CT, were not

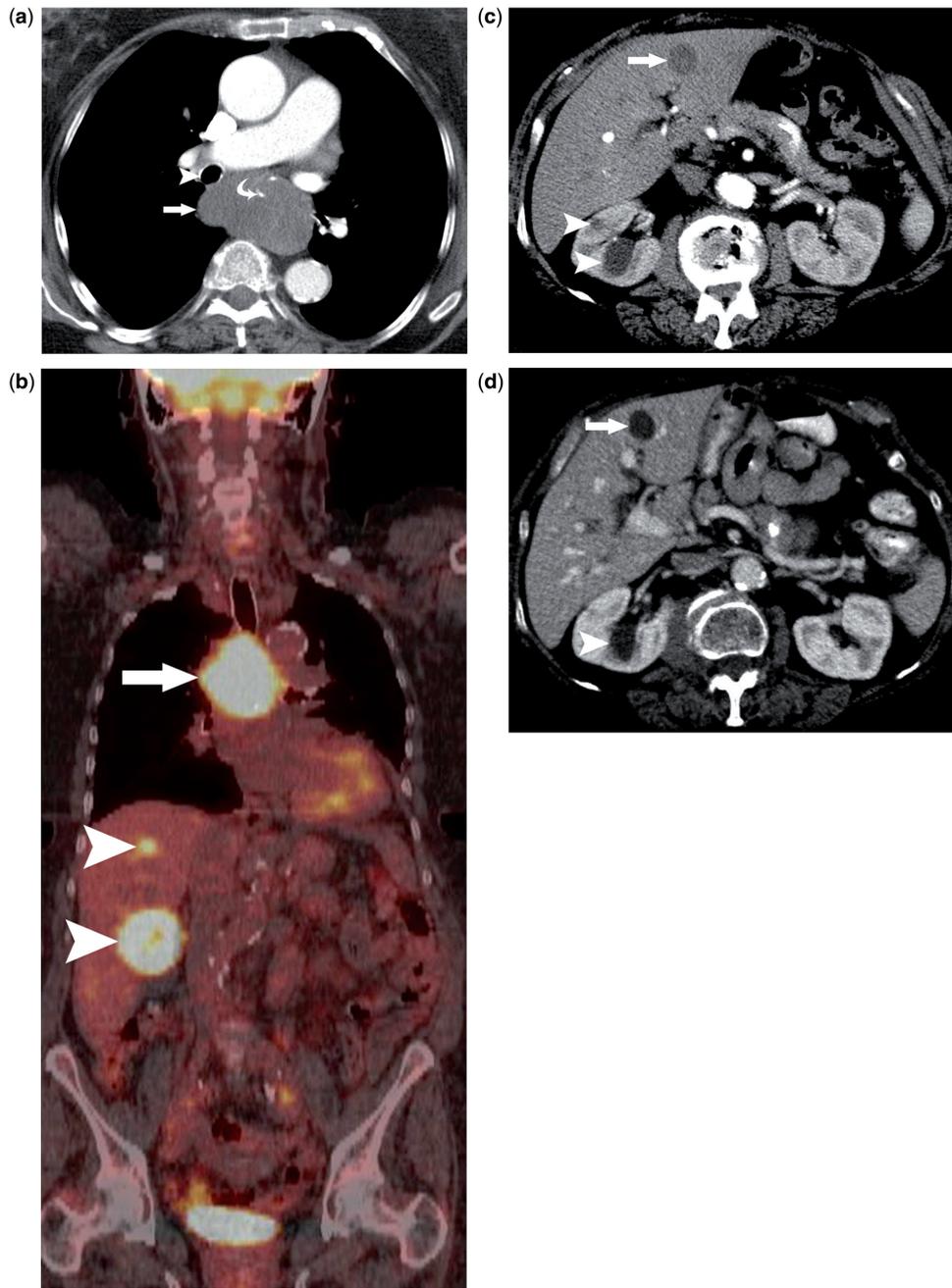
significantly FDG avid on FDG-PET/CT, and remained stable over the next 2 years. Therefore, the pulmonary nodules were not considered to be metastases.

### *Histopathologic correlation*

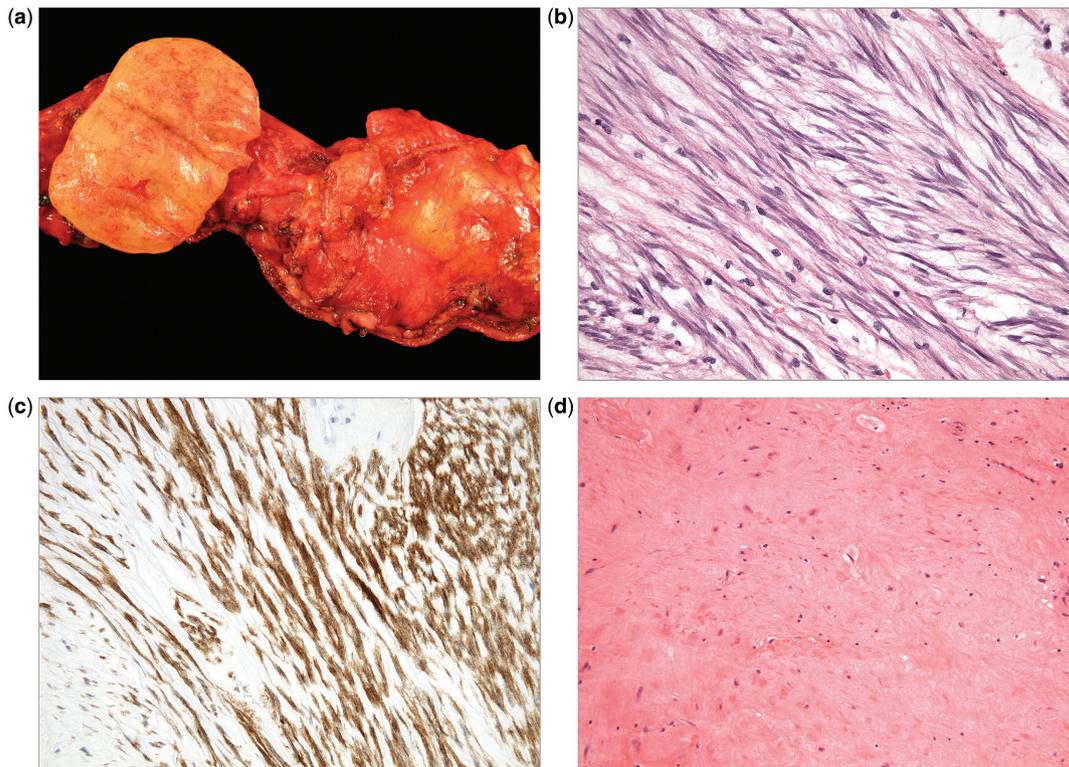
There was good correlation between the tumor size noted on CT and gross pathology. The 3 resected tumors were grossly well circumscribed (Fig. 3A). Necrosis was present in the high-risk GIST but not in the other tumors. Histologically, 6 tumors were spindle cell GISTs, composed of fascicles of elongated cells with uniform, tapering nuclei and pale eosinophilic, fibrillary cytoplasm (Fig. 3B). One tumor (case 3) was of mixed spindle cell and epithelioid type. Mitotic rate ranged from 1 to 75 per 50 HPF. Based on tumor size and mitotic activity, 4 tumors were considered high risk, and 3 were considered low risk. By immunohistochemistry, all 7 tumors were positive for KIT (Fig. 3C). CD34 was positive in each of the 6 tested patients, and 3 tumors were also positive for DOG1. Five evaluated tumors were negative for S100, 4 were negative for SMA, and 1 each was negative for desmin and caldesmon. One tumor resected after neoadjuvant imatinib therapy showed extensive stromal hyalinization, consistent with treatment effect (Fig. 3D).

### *Clinical correlation*

Three out of 7 patients underwent surgical resection of their primary tumors, and all 7 patients were treated with imatinib mesylate, primary imatinib treatment in 4 patients, adjuvant in 2 patients, and neoadjuvant followed by adjuvant in 1 patient (see details below). Two patients underwent primary surgical resection. One of these patients with a mid-esophageal tumor underwent enucleation. The surgical margins were positive, and he received adjuvant imatinib, which was discontinued after 9 months due to significant adverse effects. He is off treatment and disease free for the past 9 months. Another patient with a lower esophageal tumor underwent resection. Surgical margins were negative. He is now 34 months following surgery and continues on adjuvant imatinib without evidence of disease. The third patient who underwent surgery initially received 4 months of neoadjuvant imatinib followed by resection of lower esophageal tumor with negative margins, and adjuvant imatinib for 1 year. The patient has been treatment free and disease free for the past 27 months (total 39 months since surgery). One woman with a mid-esophageal GIST had biopsy-proven hepatic and pleural metastases at presentation and has been on primary imatinib treatment for 21 months with continued radiologic response. The fifth patient had multiple comorbidities and was not considered to be a surgical candidate. He has received primary imatinib treatment for 23 months with continued radiologic response. The sixth patient also had multiple comorbidities and was started on imatinib,



**Figure 2** (a) A 79-year-old woman with esophageal GIST. Axial image from a contrast-enhanced CT scan demonstrates a large hypoattenuating well-circumscribed exophytic mass (arrow) arising from mid-esophagus, just below the level of carina. The mass abuts the right main bronchus (arrowhead). Note the presence of calcification within the mass (curved arrow). (b) Fused [ $^{18}\text{F}$ ]FDG-PET/CT image in the coronal plane demonstrates the FDG-avid primary esophageal mass ( $\text{SUV}_{\text{max}}$  10.3) (arrow) and FDG-avid liver metastases ( $\text{SUV}_{\text{max}}$  7.6–8.6) (arrowheads). (c) Axial image from pretreatment contrast-enhanced CT demonstrates a biopsy-proven metastatic lesion in the left hepatic lobe (arrow). Attenuation value on this study was 59 HU. Right renal cysts are noted incidentally (arrowheads). (d) Axial image from a contrast-enhanced CT obtained after 2 months of imatinib treatment demonstrates unchanged size, however decreased attenuation of the liver metastasis (arrow). The attenuation value at this time was 14 HU. A right renal cyst is again noted (arrowhead).



**Figure 3** (a) Resected esophageal GIST. The tumor is grossly well circumscribed, with a homogeneous cut surface. (b) Hematoxylin and eosin stain showing a typical esophageal GIST composed of fascicles of spindle cells with elongated nuclei and pale eosinophilic, fibrillary cytoplasm. (c) By immunohistochemistry, all tumors were strongly positive for KIT. (d) After neoadjuvant imatinib therapy, the tumors showed a hypocellular appearance with marked stromal hyalinization, consistent with treatment effect.

however, the treatment was discontinued after 2 months due to severe adverse effects. The last patient received primary imatinib, and showed radiologic treatment response after 2 months. All the patients received oral imatinib 400 mg/day, except for 2 patients; 1 was started on 400 mg/day, which was reduced to 200 mg/day, and another patient was started on 200 mg/day and treatment was discontinued after 2 months, in both cases due to adverse effects.

The median follow-up period was 26 months (range 3–54 months). At present, all the patients are alive, without evidence of recurrent disease or progression of pre-existing metastatic disease.

#### *Follow-up imaging*

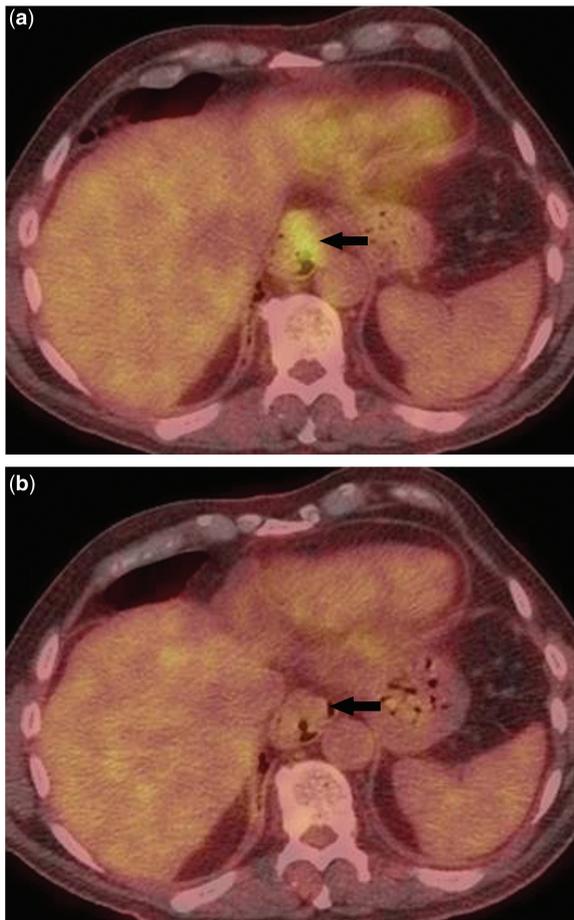
A total of 36 follow-up CTs and 1 FDG-PET/CT were reviewed. In the patient who had metastatic disease at presentation, the size of the primary tumor and metastases remained unchanged, and the attenuation values were significantly lower on follow-up imaging (Fig. 2). Three patients who did not undergo surgery showed a similar decrease in attenuation and minimal decrease in size on follow-up imaging. One patient who received 4 months of neoadjuvant imatinib prior to surgery also showed decreased attenuation of the tumor. One patient

underwent follow-up FDG-PET/CT after 2 months of imatinib treatment, which showed a significant decrease in FDG avidity of the tumor ( $SUV_{max}$  decreased from 4.5 on the baseline study to 1.2 on the follow-up examination) (Fig. 4).

## Discussion

Although GISTs are the most common sarcoma of the gastrointestinal tract, esophageal GISTs are very rare. The radiology literature about esophageal GISTs is sparse, and to the best of our knowledge, this is the first study reporting the imaging features of esophageal GIST with clinical and histopathologic correlation. In addition, treatment-related changes in the imaging appearance of primary and metastatic lesions of esophageal GIST have not been previously reported.

GISTs were originally thought to be leiomyomas or leiomyosarcomas; however, with the discovery of *KIT*-activating mutations and expression of the KIT protein, distinguishing GIST from smooth muscle tumors is now relatively straightforward in most cases by demonstrating the immunohistochemical detection of KIT (CD117). GISTs arise from the interstitial cells of Cajal in the



**Figure 4** (a) A 70-year-old man with lower esophageal GIST. Fused FDG-PET image in the axial plane before starting the treatment showing an FDG-avid mass in the lower esophagus ( $SUV_{max}$  4.5) (arrow). Physiologic uptake is noted in the bowel, kidneys, ureters and bladder. (b) Fused FDG-PET image in the axial plane after 2 months of imatinib treatment showing markedly decreased avidity of the mass ( $SUV_{max}$  1.2) (arrow). Physiologic uptake is again noted in the bowel, kidneys, ureters and bladder.

myenteric plexus (or their precursors), which play a role in gastrointestinal motility<sup>[15]</sup>.

In the pathology literature, the mean age of patients with esophageal GIST has been reported to be 63 years (range 49–75 years) with a slight male predilection<sup>[9]</sup>. The patient age in our study (mean 70 years) was similar to the prior reports, however, our patient population had a higher proportion of women (4/7). Although dysphagia has been reported to be a common presenting symptom<sup>[14]</sup>, it was noted in only 1 patient in this study. Most of the patients in this study either presented with recurrent cough or were asymptomatic.

We found a predilection for involvement of the lower esophagus (5/7), consistent with the largest available

pathologic series<sup>[9]</sup>. Esophageal GISTs can present as intraluminal, intramural or exophytic masses<sup>[9,14]</sup>. In this study, most of the patients with esophageal GIST had intraluminal masses, in contrast with GISTs at other anatomic locations, which are predominantly extraluminal<sup>[6]</sup>.

The mean largest dimension of esophageal GISTs included in our study was 5.7 cm (range 3.1–7.9 cm), compared with the previously reported size of 8 cm (range 2.6–25 cm)<sup>[9]</sup>. Based on these data, esophageal GISTs are probably similar in size at presentation to GISTs at other locations. The well-circumscribed nature, low attenuation and mild contrast enhancement of esophageal GIST are similar to those in other locations. Central necrosis was present in only 1 of our 7 patients, compared with 67% in a previously reported large imaging study of GISTs at other locations<sup>[6]</sup>. Similarly, the incidence of metastatic disease at presentation was low (1/7) in our study, which is similar to that reported in the largest pathology series of esophageal GISTs (18%, 3/17)<sup>[9]</sup>. This incidence of metastases at presentation in esophageal GIST seems to be somewhat lower than GISTs at other locations<sup>[6]</sup>. The FDG avidity of esophageal GISTs in this study (mean  $SUV_{max}$  9.5, range 4.5–12.3) was not significantly different from that previously reported for GISTs elsewhere (mean  $SUV_{max}$  5.8, range 1.4–19.7)<sup>[16]</sup>. Not surprisingly, metastatic lesions were also FDG avid.

The primary differential diagnosis of esophageal GIST on imaging is leiomyoma. Imaging features of esophageal GISTs and leiomyomas can be similar, and histopathologic diagnosis is almost always needed for confirmation<sup>[6,7]</sup>. Esophageal squamous cell carcinoma and adenocarcinoma differ from GIST in being more circumferential and infiltrative, and by having frequent nodal involvement. Lymphomatous involvement tends also to be more circumferential, but without evidence of luminal obstruction<sup>[6]</sup>.

Metastases from esophageal GIST to the liver and pleura were seen in this study. Previous studies on esophageal GIST have also reported metastases to the liver and lung<sup>[9,14]</sup>. Metastases to pleura, bone and brain from esophageal GISTs have been reported in isolated case reports<sup>[11–13]</sup>. There are insufficient data to compare the metastatic pattern of esophageal GIST with that of GISTs from other locations, which usually metastasize to liver and peritoneum, although lung metastases from GISTs arising at intra-abdominal locations are extremely rare<sup>[6,7]</sup>.

The esophageal GISTs in this study were consistently positive for KIT and CD34 by immunohistochemistry, which is consistent with previous reports<sup>[9,17]</sup>. The tumor that showed central necrosis on CT correlated with the presence of necrosis on histologic examination. This was a high-risk tumor measuring 7.5 cm in size with intense FDG uptake and showing

**Table 1** Clinical, imaging and pathologic features of patients with esophageal GISTs

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (years)/gender	64/M	79/F	71/M	61/F	70/M	87/F	56/F
Presentation	Cough	Cough	GERD	Cough	None	None	Intermittent dysphasia
Size (cm)	2.3 × 1.8	7.9 × 4.7	7.5 × 6.5	4.9 × 4.2	6.3 × 3.4	7.2 × 6.1	3.5 × 2.8
Location in esophagus	Mid	Mid	Lower	Lower	Lower	Lower	Lower
Location relative to esophageal wall	Intraluminal	Exophytic	Intramural	Exophytic	Intraluminal	Intraluminal	Intraluminal
Margin	Well defined	Well defined	Well defined	Well defined	Well defined	Well defined	Well defined
CT attenuation	Low	Low	Low	Low	Low	Low	Low
Homogeneity	Homogeneous	Homogeneous	Heterogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
FDG-PET/CT SUV <sub>max</sub>	N/A	10.3	11.7	12.3	4.5	N/A	8.7
Metastases	None	At presentation	None	None	None	None	None
Mitoses (/50 HPF)	1	2	75	1	1	1	1
Necrosis	Absent	Absent	Present	Absent	Absent	Absent	Absent
Immunohistochemistry	Positive CD34, KIT; negative SMA, S-100	Positive CD34, KIT; DOG1	Positive CD34, KIT; negative S100, SMA, caldesmon	>Positive CD34, KIT; negative S100, SMA, desmin	Positive CD34, KIT, DOG1; negative S100, SMA	Positive KIT, DOG1; negative S100	Positive CD34, KIT
Treatment	Enucleation, adjuvant imatinib	Imatinib	Resection, adjuvant imatinib	Neoadjuvant imatinib, resection, adjuvant imatinib	Imatinib	Imatinib; stopped after 2 months due to toxicity	Imatinib
Clinical outcome	NED	Stable	NED	NED	Stable	Stable	Stable
Follow-up imaging	No recurrence	Stable size, decreased attenuation	No recurrence	Stable size and decreased attenuation after neoadjuvant imatinib. No recurrence after resection	Decreased size, attenuation and SUV <sub>max</sub> after 2 months of imatinib	Stable size, decreased attenuation	Stable size, decreased attenuation

GERD, gastroesophageal reflux disease; NED, no evidence of disease.

75 mitoses per 50 HPF (an extremely high mitotic rate for GIST).

In our study, none of the patients showed disease progression or development of metastatic disease at the end of the follow-up period (mean follow-up 26 months; range 3–54 months). In prior pathology series, 56% (9/16) of patients died of disease with a median survival of 29 months (range 2–54 months)<sup>[9]</sup>. However, this study was reported in 2000, and the management of GISTs has significantly changed over the past 12 years. Furthermore, in that study, most of the patients who died of GIST had tumors larger than 9 cm, whereas all the tumors in our study were smaller than 8 cm. The management of GIST has been revolutionized in the past decade with the introduction of imatinib therapy. Imatinib, which can be used as primary, adjuvant or neoadjuvant treatment, has led to a significant increase in the median survival of patients with advanced GIST, from approximately 20 to 60 months<sup>[18–20]</sup>. Adjuvant imatinib treatment is currently recommended for 2 years following surgery, particularly in patients with large primary tumors<sup>[21]</sup>.

Both the primary and metastatic GISTs responded to imatinib treatment in the form of decreased attenuation of tumor, but with minimal decrease in size on CT. This change is similar to previously reported response patterns for GISTs at other locations, and is consistent with the treatment response described by Choi et al.<sup>[16]</sup>, who suggested that a decrease in tumor size of more than 10% or a decrease in tumor density of more than 15% on CT is a good predictor of favorable treatment response. On FDG-PET/CT, interval decrease in  $SUV_{max}$  was noted, which is also in line with previous reports<sup>[16,22]</sup>, and is considered to be good treatment response. Thus, response of esophageal GIST to imatinib therapy appears to be similar to GISTs in other locations.

The most important limitation of this study was the small sample size. However, esophageal GISTs are very rare, and there are no previous studies reporting the imaging features of GIST at this site with histopathology and clinical correlation. Due to the limited number of cases, as mentioned above, there are insufficient data to compare the clinical behavior and metastatic pattern of esophageal GIST with GISTs at other sites.

In summary, esophageal GISTs are well-circumscribed FDG-avid hypoattenuating masses that can metastasize to the liver and pleura, and respond to imatinib treatment with decreased attenuation values on CT and decreased avidity on FDG-PET/CT. Comparison with previously published data suggests that esophageal GISTs are similar in size to GISTs at other locations, but that the frequency of central necrosis and metastatic disease at presentation may be lower. Larger studies with longer follow-up will be required to determine whether the malignant potential of esophageal GISTs is different from those at other sites.

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